



A Randomized Controlled Phase II Study of Daily Online Adaptation versus Localization for MRI-Guided SBRT for Unresectable Primary or Oligometastatic Abdominal Malignancies

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Principal Investigator Signature Page

Principal Investigator (printed):

Name of Institution:

PI Signature

Date

By my signature, I agree to personally supervise the conduct of this study and to ensure its conduct in compliance with the protocol, informed consent, IRB/HRPO procedures, the Declaration of Helsinki, ICH Good Clinical Practices guidelines, and the applicable parts of the United States Code of Federal Regulations or local regulations governing the conduct of clinical studies.

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SCHEMA

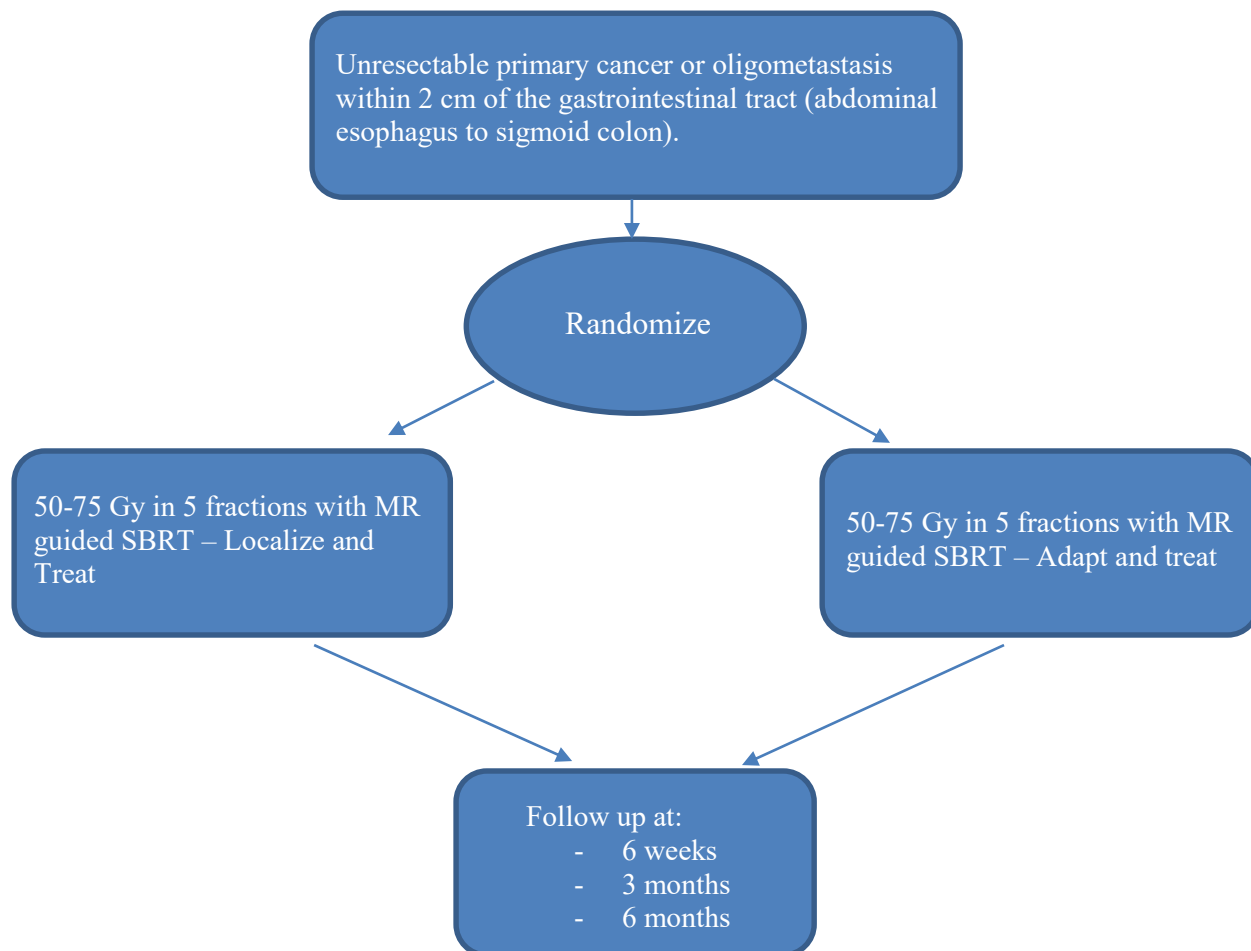


Table of Contents

SCHEMA.....	4
1.0 BACKGROUND AND RATIONALE.....	7
1.1 SBRT for Oligometastatic Disease.....	7
1.2 SBRT for Unresectable Primary Abdominal Disease.....	8
1.3 Organ Motion and Adjacent Critical Structures.....	8
1.4 Tumor Localization and Intrafractional Tumor Motion.....	9
1.5 Online Adaptive Radiation Therapy.....	9
1.6 Study Rationale.....	12
2.0 OBJECTIVES.....	12
2.1 Primary Objective.....	12
2.2 Secondary Objectives.....	12
2.3 Exploratory Objective.....	13
3.0 PATIENT SELECTION.....	13
3.1 Inclusion Criteria.....	13
3.2 Exclusion Criteria.....	13
3.3 Inclusion of Women and Minorities.....	14
4.0 REGISTRATION PROCEDURES.....	14
4.1 Confirmation of Patient Eligibility.....	14
4.2 Patient Registration in Siteman Cancer Center OnCore Database.....	14
4.3 Assignment of UPN.....	15
4.4 Randomization.....	15
5.0 TREATMENT PLAN.....	15
5.1 Radiation Therapy Guidelines.....	15
5.2 Evaluability Guidelines.....	17
5.3 General Concomitant Medication and Supportive Care Guidelines.....	17
5.4 Women of Childbearing Potential.....	17
5.5 Duration of Therapy.....	17
5.6 Duration of Follow-up.....	18
6.0 REGULATORY AND REPORTING REQUIREMENTS.....	18
6.1 Definitions.....	18
6.2 Reporting to the Human Research Protection Office (HRPO) at Washington University.....	20
6.3 Reporting to the Quality Assurance and Safety Monitoring Committee (QASMC) at Washington University.....	20
6.4 Reporting Requirements for Secondary Sites.....	20
6.5 Reporting to Secondary Sites.....	21
6.6 Timeframe for Reporting Required Events.....	21
7.0 CORRELATIVE STUDIES.....	21
8.0 STUDY CALENDAR.....	22
9.0 DATA SUBMISSION SCHEDULE.....	22
10.0 MEASUREMENT OF EFFECT.....	23
10.1 Antitumor Effect – Solid Tumors.....	23
10.2 Disease Parameters.....	23
10.3 Methods for Evaluation of Measurable Disease.....	24
10.4 Response Criteria.....	26
11.0 DATA AND SAFETY MONITORING.....	27
12.0 AUDITING.....	29
13.0 STATISTICAL CONSIDERATIONS.....	29
13.1 Stopping Criteria.....	29
13.2 Sample Size.....	29
13.3 Primary Objective.....	30

13.4	Secondary Objectives.....	30
13.5	Statistical Analysis Plan.....	30
14.0	MULTICENTER REGULATORY REQUIREMENTS.....	31
15.0	REFERENCES	32
APPENDIX A: ECOG Performance Status Scale		35

1.0 BACKGROUND AND RATIONALE

1.1 SBRT for Oligometastatic Disease

Despite advances in cancer therapy, metastatic disease is an eventual reality for innumerable oncology patients. Historically, the prevailing notion was that patients with such systemic disease benefit primarily from systemic therapies. Local therapies were employed solely for palliation and symptom management. However, over the past two decades, there has been increasing evidence of an intermediate stage between local disease and disseminated systemic metastases. In this “oligometastatic state,” cancerous cells first metastasize to a few discrete sites before gaining widespread metastatic potential.(1) Theoretically, ablation of these discrete metastases before further transformation of malignant clones would then produce a durable survival in addition to local control. The validity of this theory and the efficacy of local intervention to slow the progression of systemic disease have since been demonstrated by numerous studies.(2-5)

Within the realm of radiation therapy, stereotactic body radiotherapy (SBRT) has emerged as one such means to locally target metastatic disease. SBRT has several characteristics that make it a highly attractive treatment modality for extracranial metastases. First, unlike alternative methods of “metastasectomy” (such as surgery, radiofrequency ablation (RFA), or chemoembolization), SBRT is non-invasive. SBRT is also preferable to conventionally fractionated radiotherapy (CFRT) because it delivers high doses of radiation in a hypofractionated course (up to 5 fractions, by definition) and achieves a higher biologically effective dose (BED) than CFRT. This allows for ablation of the target tissue over a period of just 1-2 weeks.(6-8) Finally, SBRT is highly conformal, with rapid dose fall-off, providing the capacity to minimize toxicity from damage to surrounding normal structures.

SBRT has potential to allow durable survival in carefully selected patients with oligometastatic disease. In-field control rates of metastases treated with SBRT are roughly 80% up to four years after therapy, even in series examining heterogeneous histologies, sites, and dose.(9-11) Although a majority of patients who undergo SBRT for oligometastatic disease will experience relapse with distant metastases, approximately 20% of patients with in-field control remain disease-free at 2-4 years of follow-up.(9, 10, 12) In a prospective study by Milano et al., 24% of patients treated with SBRT for oligometastases (five or fewer sites) remained free of disease at last follow-up, with a median follow-up time of 36 months.(9) Of those patients who experience recurrence, as many as 60% have very limited metastatic progression that could be amenable to further intervention such as repeated SBRT.(13) Epidemiologic data suggests that patients undergoing such repetitive metastasectomy have a survival benefit that is comparable to those undergoing their first procedure.(14)

Further dose escalation in SBRT may improve local control and might offer improvement in durable survival. In the oligometastatic state, disease-free survival (DFS) is contingent upon successful local ablation of metastases to halt the development of malignant clones with widely metastatic potential. The validity of this concept is highlighted by a pooled analysis of patients who underwent surgical resection for lung metastases. Those who underwent incomplete metastasectomy had a median survival of only 15 months, in contrast with 35 months for patients who had complete metastasectomy.(15) With regards to SBRT, success of metastasectomy by local ablation depends on dose. Several SBRT dose escalation trials have demonstrated that increased dose increases local control, with reported rates up to 100% at 12 months follow-up.(10, 16-18) It is logical, then, that further dose escalation above current fractionation schemes could improve in-field ablation and control beyond the average 80% and in turn, increase the incidence and duration of disease-free survival.

1.2 SBRT for Unresectable Primary Abdominal Disease

Apart from its applications for oligometastatic disease, SBRT has been increasingly used for treatment of abdominal malignancy, such as unresectable liver and pancreas tumors. In the treatment of primary and metastatic liver lesions, the use of SBRT has increased dramatically over the past half decade. Several recent institutional studies have demonstrated the efficacy and relative safety of dose-escalated SBRT to the liver for hepatocellular carcinoma (HCC). In 2011, Andolino et al. successfully dose-escalated treatment to patients with primary HCC to a dose schedule of 48Gy in 3 fractions and 40 Gy in 5 fractions, depending upon the patients' underlying liver function (Child-Pugh Class A versus Class B). Complete response (CR) and partial response (PR) rates by RECIST criteria were good at 30% and 40% respectively (median 27 months follow-up). However, while tolerable overall, treatment led to progression in Child-Pugh scores (worsening of underlying liver function) by a median of 20%.⁽¹⁹⁾ In a larger study of SBRT for HCC, Dawson et al. used a more conservative, six-fraction approach to treat inoperable disease to a median of 36.6 Gy. This regimen improved toxicity outcomes, but local response rates suffered, with a 11% CR and 33% PR at one year follow up.⁽²⁰⁾ Both studies employed normal tissue complication probability (NTCP) modeling in order to maximize safety of treatment delivery based on the patients' underlying liver function. However, NTCP modeling does not account for organ motion or the proximity of adjacent critical structures, which remain a significant factor in the safe and effective high-dose treatment of HCC with SBRT. It is possible that with improved tumor localization, tumor tracking, and adaptive planning, reduced target volumes and a dose schedule permitting both excellent local control and low levels of toxicity could be achieved.

Similar to the expanding use of SBRT for liver lesions, multiple institutions have implemented SBRT for the treatment of unresectable pancreatic cancer. As a treatment modality, SBRT is attractive in that it reduces the course length of radiotherapy to one week, minimizing chemotherapy breaks. SBRT also offers the potential for high-dose ablative therapy for a disease that has been marginally responsive to conventionally fractionated radiation. Presently, investigators have safely achieved dose schedules of 30-40 Gy/5 fractions for treatment of pancreatic cancer. ^(21, 22) While such dose schedules limit toxicity, the biologically equivalent dose (BED) achieved is less than 100Gy. Achievement of a BED >100 Gy has been shown to be critical in the long-term disease control using SBRT in other disease sites, such as lung cancer. ^(17, 23)

1.3 Organ Motion and Adjacent Critical Structures

High-dose treatment of oligometastatic or unresectable primary abdominal malignancy with SBRT has been historically limited by toxicity to surrounding normal tissues. This is of particular concern in the abdomen because tumors are often adjacent to eloquent structures and are strongly affected by organ motion. Abdominal planning constraints are based in great part upon the observed delicacy of immediately adjacent critical structures. In pancreatic cancer, the proximity of organs such as duodenum and small bowel have led to identification of conservative point dose constraints, such as 23 Gy to 1cc of the duodenum, that predict for toxicity outcomes.⁽²⁵⁾ While protecting patients from toxicity, such constraints severely limit delivery of sufficiently ablative dose to pancreatic tumors, which often physically efface portions of bowel. As a result of the necessary trade-off between tumor coverage and sparing of organs-at-risk, there is frequent variability in achievable delivered dose to abdominal disease. In a recent review of SBRT for abdominal oligometastases; Almaghrabi et al examined use of SBRT for liver, adrenal, and paraaortic lesions. They noted use of highly variable dose schedules and frequent toxic events, without clear consensus on optimal dose, number of fractions, or planning constraints.⁽²⁴⁾ High

quality daily setup imaging with appropriate soft-tissue definition and the ability to change the treatment plan at the time of treatment, based on observed daily anatomy, could improve the precision and accuracy of dose delivery to target volumes with avoidance of adjacent eloquent structures. This improved precision and accuracy in SBRT could preserve protection of organs-at-risk, and simultaneously enable improved tumor coverage, in the face of previously dose-limiting toxicity constraints.

Apart from collateral damage to adjacent critical structures, dose escalation in SBRT is also limited by toxicity secondary to organ motion. This is especially true in treatment of abdominal lesions, where treatment planning must account for motion related to the respiratory cycle. In a phase II study by Hoyer et al. of SBRT to inoperable pancreatic tumors, 79% of patients progressed to at least grade 2 toxicity, with 23% of patients experiencing grade ≥ 3 toxicities.(26) Although this is a higher rate of toxicity for abdominal SBRT than has been reported by other groups, Hoyer et al. used larger margins (10 mm longitudinally and 5 mm transversely) in an attempt to better account for target motion with respiration. For abdominal lesions, smaller margins might limit toxicity, but could also compromise local control. While SBRT is capable of delivering highly conformal, ablative doses with rapid dose fall off, these studies illustrate that safe and successful treatment of oligometastases with SBRT also depends on accurate target delineation. Development of corresponding technology to accurately localize tumors and eliminate the uncertainty of organ movement during treatment has potential to allow safe dose escalation with SBRT beyond current treatment paradigms.

1.4 Tumor Localization and Intrafractional Tumor Motion

Presently, several technologies are employed to bridge the gap between SBRT conformality and tumor localization, but they are insufficient. Four-dimensional computed tomography (4DCT) combined with external respiratory surrogates permits “binning” of planning images to generate patient-specific internal margins. Ideally, 4DCT-based internal target volumes (ITV) and planning would account for intrafractional tumor motion and reduce organ motion artifacts. However, ITV instability has been demonstrated to range from 46% to 127% for tumors as small as 1cm in diameter.(27) Similarly, a study by Ge et al. comparing planning abdominal 4DCT for 10 patients to fluoroscopic movies of daily intrafractional tumor motion found that 4DCT provided inadequate representation of daily motion of abdominal tumors during treatment.(28)

The range of day-to-day variation in positions of abdominal tumors has also been well studied. In a study by Shinoki et al. 15 patients underwent repeat 4DCT during radiation therapy. Over the course of therapy, the range of motion of the pancreas, as measured by biliary stent position, could exceed 1 cm in each direction, a finding that has since been re-demonstrated. (29, 30) This degree of pancreatic and abdominal motion highlights the importance of daily tumor localization for abdominal SBRT. The logical next step is real-time imaging of target tissues to reliably track motion and permit daily adjustments of treatment plans. Such adaptive planning on the basis of real-time monitoring is needed to improve SBRT accuracy and enable dose escalation.

1.5 Online Adaptive Radiation Therapy

Adaptive radiation therapy (ART) has dosimetric benefits that make it an appealing modality for SBRT treatment planning, but it has only recently been implemented, clinically (31, 32). ART, or the practice of adjusting a patient’s daily radiotherapy plan in response to observed changes in the geometry of the treatment target or surrounding tissues, is generally implemented on the basis of imaging feedback. Successful use of “offline” adaptive radiation therapy (ART), or re-planning of treatment after the patient is off the treatment table, has been reported in the treatment of prostate,

head and neck, and lung cancers. These reports demonstrate that offline ART leads to reduction of treatment volumes and permits dose escalation with comparable toxicity to prior, lower dose RT studies of the same sites.(33-35)

The feasibility of online-adaptive, MR-guided, intensity-modulated radiation therapy (IMRT) has recently been established, as has the feasibility of non-adaptive MR-guided SBRT to the liver.(32, 36, 37) However, feasibility of MR-guided, online-adaptive SBRT has yet to be reported. While there is limited published experience of clinical use of ART for SBRT or for oligometastases, its appeal for such a treatment scenario is straightforward to appreciate. ART for SBRT would improve target coverage while also reducing treatment volumes and protecting normal tissues. The potential dosimetric benefits of “online” adaptive SBRT, defined as adjustment and delivery of a new daily SBRT plan while the patient is still on the treatment table, have recently been demonstrated by Henke et al. When compared to actual image-guided daily repositioning of SBRT plans for 10 patients with oligometastatic or unresectable primary malignancy of the central thorax and abdomen, simulations of online adaptive SBRT plans using MR image-sets demonstrated significant improvements in both target coverage and normal tissue sparing.(38) In patients with oligometastatic disease, MR-guided online-adaptive SBRT would create an opportunity for dose escalation with potential improved local control and survival benefits, without increasing toxicity.

Although the feasibility of MR-guided, online-adaptive SBRT has yet to be published in the literature, an ongoing institutional pilot study at Washington University in St. Louis (HRPO# 201410002) is nearing completion and preliminary results demonstrate feasibility of this treatment technique as well as potential reductions in acute toxicity with uncompromised local control. Overall treatment time is increased by at least 30 minutes compared with patients treated with similar doses without plan adaptation. This pilot study included patients with oligometastatic or unresectable non-liver abdominal malignancy. Compared to historical controls with similar high dose treatment, where acute grade 3 or greater GI toxicities have been reported to be as high as 25-35%, preliminary 3-month data demonstrates zero cases of Grade 3 or higher acute GI toxicity, with a risk-adapted dose of 50Gy/5 fractions.(26, 39) This early evidence supports the hypothesis that online-adaptive MRI-guided SBRT could reduce toxicity while opening the opportunity for dose-escalation and improved disease control, offering durable survival advantage.

1.5.1 MRI-Based ART

Implementation of adaptive planning for SBRT requires real-time feedback imaging with high 3D spatial accuracy and tissue contrast definition, without disruption of radiation delivery. Until recently, that technology has not existed. However, MRI-based online adaptive radiotherapy and delivery is now clinically available at participating institutions using an integrated MRI-Co-60 treatment device (Viewray System, Viewray Inc, Cleveland, OH).(31)

MRI-based planning, tracking, and gating are not only feasible for SBRT for the treatment of oligometastases, but also offer significant advantages over conventional, CT-based treatments. With respect to planning, MRI reduces intra-observer variability in target contouring and provides better soft tissue characterization compared to CT, which makes it ideally suited for segmentation of visceral metastases.(40) Although many institutions use fusions of CT and MRI images in initial treatment planning, use of MRI-simulation alone has been limited by concern over geometric distortions of MR and the complexities of determining of electron density information without CT. These historical

obstacles have been all but eliminated by modern advancements. Nyholm et al. found that after standard corrections, uncertainty from MR geometric distortions translated to a maximum error of only 1mm. In fact, by eliminating the need for CT and MRI registration, treatment planning directly on MR images actually reduced spatial uncertainty when compared to CT-based radiotherapy.(41)

Successful MRI planning, paired with delivery of MRI-guided radiation therapy to the abdomen is now possible with an integrated MRI-Co-60 device. For on-board imaging, tumor tracking, and gated treatment delivery with MRI, the greatest historical obstacle has been the interaction between the magnetic field, treatment beam, and device hardware. Viewray (Cleveland, Ohio) has produced a unique MRI-radiation unit, consisting of Co-60 gamma ray IMRT unit combined with an open, split solenoid 0.35 T MRI scanner capable of parallel imaging. The MRI component is designed as a low-field unit to eliminate significant disruptions of the dose distributions and limit magnetic susceptibility artifacts due to the patient to enable imaging with spatial integrity. Its efficacy and capacity to produce scans of sufficient quality for clinical analysis has already been demonstrated; it is a variant of the Siemens MAGNETOM device used for intraoperative imaging. It is capable of not only volumetric imaging for localization, but also cine MRI imaging at a rate of 4 frames per second during radiation delivery. Such continuous cine MRI permits detailed, non-invasive target tracking with excellent soft-tissue definition during of radiation. The Viewray system, which combines this imaging unit with three Co-60 heads distributed equally 120 degrees apart, will gate treatment to turn the radiation on or off based on the cine images acquired every 0.25 seconds. Viewray's device also incorporates a double-focused multileaf collimator for intensity modulation of the gamma rays. Commissioning and testing of treatment planning software, dose delivery, and imaging for this device have been completed and several institutions worldwide now use this device for standard-of-care patient treatment.(42-44) Its potential to measurably improve the delivery and clinical outcomes of SBRT is striking, but has not been fully evaluated. The greatest current limitations to improving SBRT, like precise tumor volume delineation and lack of ability to sufficiently account for known target movement and deformation, are addressed and potentially overcome by the Viewray system.

On-board MRI imaging is superior to current on-board kilovoltage imaging. Previously, post-planning daily imaging for treatment setup has presented significant challenges in target definition of oligometastatic disease, especially for soft-tissue, visceral metastases that are poorly defined by kV images. This is particularly important in treatment sites such as the central thorax, liver, and non-liver abdomen, where target definition is both critical for avoidance of normal structures and challenging due to organ motion. Traditionally, surrogate markers like internal fiducials and bony anatomical landmarks have been used to supplement on-board kV images to confirm positional accuracy and permit gating. However, a pilot study at our institution (HRPO# 201105295) has demonstrated that the low-field imaging component of the Viewray machine provides better critical structure identification than on-board kV imaging. This was especially true in the abdomen and the central thorax.(45) This improvement in imaging quality, along with reduction in planning error from registration of planning MRI to daily kV images and conversion between imaging modalities, will make Viewray's MR component an asset to the treatment of oligometastases with SBRT.

Although Co-60 treatment planning and delivery systems have been previously implemented for stereotactic radiation (such as the gamma knife surgery), quality

assurance is critical and has been thoroughly addressed by participating institutions for the implementation of the Co-60 treatment planning and delivery system component of the Viewray machine.(43) FMEA analysis to identify key risks for QA of adaptive radiotherapy using the integrated Viewray system as well as RPN scoring to determine critical QA steps were performed and mitigation was determined. Onsite physicians will mitigate autosegmentation error, while onsite physicists will mitigate plan errors in automatically generated adaptive plans and assess change in fluence between the original plan and the adaptive plan to prevent non-optimized plan delivery. The largest source of error in adaptive planning, generally, is related to communication and data transfer between devices and systems.(46) Fortunately, this is avoided in our treatment paradigm, as the Viewray treatment planning software, radiation therapy system, and imaging unit are fully integrated, with confirmation of patient setup easily verified with high resolution, volumetric MRI imaging. An online QA process will be implemented prior to treatment for all new daily adaptive plans.

1.6 Study Rationale

In light of this new technology and preliminary findings of low toxicity of online, adaptive, MR-guided stereotactic radiation on a single arm prospective study, we propose to compare this technique to online MR-guided SBRT without adaptation. Online plan adaptation increases treatment times for patients and comprises an increased burden on technical and clinical staff. Although preliminary trial results are encouraging, it remains unclear if the dosimetric benefits of online-adaptive planning studies will translate to measurable improvements in clinical outcomes that merit its routine use. In our preliminary study, plan adaptation was most often required when tumors were adjacent to the gastrointestinal tract (the esophagus to the sigmoid colon), as those structures were most commonly the dose-limiting structures and were noted to change in location on a day-to-day basis. For these reasons, abdominal disease sites have historically highlighted the limitations of SBRT. Specifically, we will enroll patients with oligometastatic or unresectable primary disease of the non-liver abdomen to a randomized, prospective trial.

Patients will be randomized to one of two treatment arms, in which they will receive either online-adaptive, MRI-guided SBRT or non-adaptive MRI-guided SBRT. Both patient groups will undergo MRI simulation and MRI treatment localization with online MR monitoring and/or gating. All patients will be treated in five fractions over one to two weeks. By adhering to strict normal tissue constraints, we expect toxicity to be within the current standard of care for the non-adaptive arm, with reduction in toxicity in the arm of patients who undergo adaptation based on daily anatomic changes.

2.0 OBJECTIVES

2.1 Primary Objective

To determine the incidence of non-hematologic acute grade 3 or greater toxicity occurring in patients receiving online, adaptive, MRI-guided SBRT to the abdomen and in patients receiving non-adaptive SBRT through 6 months post-start of treatment.

2.2 Secondary Objectives

1. To determine the local, in-field failure free rate at six months follow-up.
2. To determine the progression free survival rate at six months follow-up.

3. To determine the rate of overall survival at six months follow-up.

2.3 Exploratory Objective

To evaluate the change in patient-reported quality of life from baseline to 6 weeks and to 6 months post-treatment using EORTC-30 criteria.

3.0 PATIENT SELECTION

3.1 Inclusion Criteria

1. Oligometastatic disease or unresectable primary abdominal malignancy with biopsy-proven primary disease histology of solid tumor categorization. Patients with a diagnosis of hepatocellular carcinoma do not require a biopsy.
2. No more than three progressive sites of disease, with at least one of the disease sites to be deemed suitable for treatment with MRI-guided, online adaptive SBRT to the non-liver abdomen as per radiation oncology evaluation.
3. Must be treated per protocol to lesion(s) of a single abdominal site that can reasonably be encompassed within a single treatment field. Treatment of additional site(s) outside of the abdomen while the patient is on trial is acceptable.
4. The treated lesion must be within 2 cm of the abdominal gastrointestinal tract (abdominal esophagus to sigmoid colon) on the basis of cross sectional imaging study such as CT, PET/CT, or MRI.
5. Must be deemed medically fit for SBRT by the treating physician.
6. At least 18 years of age.
7. ECOG performance status of 0 or 1 (see Appendix A)
8. Must have completed any systemic therapy at least one week prior to planned start of SBRT (two weeks preferred), and must have no plans to initiate systemic therapy for at least one week following end of SBRT (two weeks preferred).
9. Women of childbearing potential and men must agree to use adequate contraception (hormonal or barrier method of birth control, abstinence) prior to study entry and for the duration of study participation. Should a woman become pregnant or suspect she is pregnant while participating in this study, she must inform her treating physician immediately.
10. Able to understand and willing to sign an IRB approved, written informed consent document (or that of legally authorized representative, if applicable).

3.2 Exclusion Criteria

1. Primary disease of hematologic origin, lymphoma, or small cell cancer.
2. Past history of external beam radiotherapy within the projected treatment field of any of the

disease sites to be treated by MRI-guided, online adaptive SBRT.

3. Currently receiving any other investigational agents.
4. Uncontrolled intercurrent illness including, but not limited to, ongoing or active infection, symptomatic congestive heart failure, unstable angina pectoris, or cardiac arrhythmia.
5. Pregnant and/or breastfeeding. Patient must have a negative pregnancy test within 14 days of study entry.
6. Medical contraindication to undergoing MR imaging.

3.3 Inclusion of Women and Minorities

Both men and women and members of all races and ethnic groups are eligible for this trial.

4.0 REGISTRATION PROCEDURES

Patients must not start any protocol intervention prior to registration through the Siteman Cancer Center.

The following steps must be taken before registering patients to this study:

1. Confirmation of patient eligibility by Washington University
2. Registration of patient in the participating Cancer Center database
3. Assignment of unique patient number (UPN)

Once the patient has been entered in the Siteman Cancer Center OnCore database, the WUSM coordinator will forward verification of enrollment and the UPN via email.

4.1 Confirmation of Patient Eligibility

Confirm patient eligibility by collecting the information listed below and scanning and emailing it to the Washington University research coordinator at least one business day prior to registering the patient:

1. Your name and contact information (telephone number, fax number, and email address)
2. Your site PI's name, the registering MD's name, and your institution name
3. Patient's race, sex, and DOB
4. Three letters (or two letters and a dash) for the patient's initials
5. Currently approved protocol version date
6. Copy of signed consent form (patient name may be blacked out)
7. Planned date of enrollment
8. Completed eligibility checklist, signed and dated by a member of the study team
9. Copy of appropriate source documentation confirming patient eligibility

4.2 Patient Registration in Siteman Cancer Center OnCore Database

Registrations may be submitted Monday through Friday between 8am and 5pm CT. Urgent late afternoon or early morning enrollments should be planned in advance and coordinated with the

Washington University research coordinator. Registration will be confirmed by the research coordinator or his/her delegate by email within one business day. Verification of eligibility and registration should be kept in the patient chart.

All patients at all sites must be registered through the Siteman Cancer Center OnCore database at Washington University.

4.3 Assignment of UPN

Each patient will be identified with a unique patient number (UPN) for this study. Patients will also be identified by first, middle, and last initials. If the patient has no middle initial, a dash will be used on the case report forms (CRFs). All data will be recorded with this identification number on the appropriate CRFs.

4.4 Randomization

Patients will undergo 1:1 randomization between MR-guided SBRT, with online plan adaptation, versus MR-guided SBRT with MR-localization only and non-adaptive planning. A computer-generated randomization scheme (maintained centrally by the study statistician) will be used to assign subjects.

5.0 TREATMENT PLAN

5.1 Radiation Therapy Guidelines

5.1.1 Dose, Fractionation

All patients will be initially planned for stereotactic body radiation therapy to a minimum dose of 50-75 Gy in five fractions to the PTV, subject to the same, pre-defined hard constraints for organs-at-risk below (Section 5.1.5). Radiotherapy will consist of stereotactic body therapy, to be given over five fractions, delivered once daily or once every other day for a period of one to two weeks, for a total of five treatments. Patients will be 1:1 randomized to receive either non-adaptive MR-guided SBRT or online-adaptive MR-guided SBRT.

5.1.2 Simulation Procedures/Patient Positioning

All patients will undergo both CT and MRI simulation in positioning appropriate for the specific treatment site. When medically feasible and applicable, patients will be simulated with IV and small bowel contrast.

5.1.3 Clinical Target Volume (CTV) and Planning Target Volume (PTV) Definitions

The treatment target will be defined based on the gross tumor volume (GTV) only. No CTV expansion will be utilized. The PTV will be generated at the discretion of the treating physician but should range between 3 mm and 7 mm.

5.1.4 Initial Treatment Planning

All patients will be initially planned to 50-75 Gy in 5 fractions, subject to hard constraints based on the treatment site. Dose volume histogram (DVH) information for the target volumes and surrounding critical structures is mandatory. This is to assist in interpreting outcome, including morbidity. Coverage goal will be for 95% of the volume to be covered by 95% of the dose, although in situation where a critical structure is violated, reduction of dose will be allowed in areas of overlap. For specific hard constraints and optimization parameters, see Table 1. Initial treatment plans will be centrally reviewed by a trial PI prior to treatment initiation, to ensure that DVH criteria are met and to review plan conformality.

5.1.5 SBRT Dose Constraints

These shall function as hard constraints in treatment planning, and coverage will be sacrificed in order to meet these constraints.

Non-liver Abdomen Site Treatment Planning Constraints	
Structure	Goal
PTV	95% coverage by 95% of Rx dose
Uninvolved liver (liver - GTV)	700 cc < 20 Gy
	V25Gy < 33%
	Mean < 20 Gy
Duodenum max	V36Gy \leq 0.5 cc
Stomach max	V36Gy \leq 0.5cc
Small bowel max	V36Gy \leq 0.5 cc
Large bowel max	V36Gy \leq 0.5 cc
Cord	V25Gy < 0.5cc
Kidney (combined)	Mean < 18 Gy
Esophagus max	V36Gy \leq 0.5 cc
Heart/Pericardium	V32Gy \leq 15 cc

5.1.6 Adaptive Treatment Planning and Evaluation

When patients present for their first SBRT treatment session, the treating physician will evaluate their individual anatomy to determine if adaptive planning is indicated. Patients randomized to the online-adaptive treatment planning arm will have all tumor volumes and critical structures within 3 axial slices of the PTV re-contoured on the MR-localization image of the day. The estimated delivered dose should be calculated using the software on the console. An adapted radiation therapy plan should be generated based on the following guidelines:

- 1) The V36 of the gastrointestinal structures (abdominal esophagus to sigmoid colon) is greater than or equal to 1.0 cc.
- 2) The volume receiving 95% of the prescription dose of the PTV is 10% less than what was calculated on the original plan.
- 3) The volume receiving 95% of the prescription dose of the PTV or CTV was less than or equal to 85% and there is a favorable shift in the dose-limiting organ at risk, such that adaptive planning would improve the volume receiving 95% of the prescription

dose of the PTV or CTV by 10% or more.

After generation of an adapted radiation therapy plan, the plan should be normalized to meet the gastrointestinal structure tissue constraint of V36 Gy < 0.5cc.

5.1.7 Quality Assurance of the Adaptive Plan

Patient specific QA will be performed at each fraction prior to delivery of the adaptive treatment plan based on institutional standards. Given that physical dose measurements will not be possible with the patient on the table, this can be achieved by performing an independent Monte Carlo dose calculation on the image of the day, using the exported beam parameters, and mapped electron density. A final review by physics will be required prior to proceeding to treatment delivery.

5.2 Evaluability Guidelines

All patients who receive any radiation therapy are evaluable for the primary objective (toxicity).

Patients who complete at least one fraction of MR-guided radiation therapy are evaluable for the secondary objectives relating to tumor response, control rate, and survival rates.

Patients randomized to adaptive therapy who are unable to complete treatment in that arm will finish treatment based on the discretion of the treating physician, and toxicity and outcome endpoints will be recorded and analyzed under an “intention to treat” model.

5.3 General Concomitant Medication and Supportive Care Guidelines

Patients are not permitted to receive systemic therapy beginning one week prior to start of SBRT and continuing through SBRT and one week post-completion of SBRT. (It is preferred that patients do not receive systemic therapy within 2 weeks of starting and ending SBRT, but that is left to the discretion of the treating physician.)

5.4 Women of Childbearing Potential

Women of childbearing potential (defined as women with regular menses, women with amenorrhea, women with irregular cycles, women using a contraceptive method that precludes withdrawal bleeding, and women who have had a tubal ligation) are required to have a negative pregnancy test within 14 days prior to the start of SBRT.

If a patient is suspected to be pregnant, SBRT should be immediately discontinued. In addition a positive urine test must be confirmed by a serum pregnancy test. If it is confirmed that the patient is not pregnant, the patient may resume dosing.

If a female patient or female partner of a male patient becomes pregnant during therapy, the investigator must be notified in order to facilitate outcome follow-up.

5.5 Duration of Therapy

If at any time the constraints of this protocol are considered to be detrimental to the patient's health and/or the patient no longer wishes to continue protocol therapy, the protocol therapy should be discontinued and the reason(s) for discontinuation documented in the case report forms.

In the absence of treatment delays due to adverse events, treatment may continue for up to 5 fractions (5 days of SBRT) or until one of the following criteria applies:

- Death
- Adverse event(s) that, in the judgment of the investigator, may cause severe or permanent harm or which rule out continuation of study drug
- General or specific changes in the patient's condition render the patient unacceptable for further treatment in the judgment of the investigator
- Suspected pregnancy
- Serious noncompliance with the study protocol
- Lost to follow-up
- Patient withdraws consent
- Investigator removes the patient from study
- The participating Cancer Center decides to close the study

If there is a treatment delay of more than 10 days, the patient will be taken off study and followed under the intention to treat. Patients who prematurely discontinue treatment for any reason will be followed as indicated in the study calendar.

5.6 Duration of Follow-up

Patients will be followed for 6 months following the completion of SBRT or until death, whichever occurs first. Patients removed from study for unacceptable adverse events will be followed until resolution or stabilization of the adverse event. Follow-up will consist of routine volumetric imaging at 4-8 weeks, 3-5 months, and 6-8 months post-completion of SBRT to evaluate treatment response, and evaluation of QOL (as described in Section 7.0) at 6 weeks and 6 months post-completion of SBRT. Any additional follow-up and imaging will be obtained off-study as per routine clinical policies of the treating physician.

6.0 REGULATORY AND REPORTING REQUIREMENTS

The entities providing oversight of safety and compliance with the protocol require reporting as outlined below. The Washington University Human Research Protection Office (HRPO) requires that all events meeting the definition of unanticipated problem or serious noncompliance be reported as outlined in Section 6.2.

6.1 Definitions

6.1.1 Adverse Events (AEs)

Definition: any unfavorable medical occurrence in a human subject including any abnormal sign, symptom, or disease.

Grading: the descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized for all toxicity reporting. A copy of the CTCAE version 4.0 can be downloaded from the CTEP website.

Attribution (relatedness), Expectedness, and Seriousness: the definitions for the terms listed that should be used are those provided by the Department of Health and Human Services' Office for Human Research Protections (OHRP). A copy of this guidance can be found on OHRP's website:

<http://www.hhs.gov/ohrp/policy/advevntguid.html>

6.1.2 Serious Adverse Event (SAE)

Definition: any adverse drug experience occurring at any dose that results in any of the following outcomes:

- Death
- A life-threatening adverse drug experience
- Inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant disability/incapacity (i.e., a substantial disruption of a person's ability to conduct normal life functions)
- A congenital anomaly/birth defect
- Any other experience which, based upon appropriate medical judgment, may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed above

6.1.3 Unexpected Adverse Experience

Definition: any adverse drug experience, the specificity or severity of which is not consistent with the current investigator brochure (or risk information, if an IB is not required or available).

6.1.4 Life-Threatening Adverse Experience

Definition: any adverse drug experience that places the subject (in the view of the investigator) at immediate risk of death from the reaction as it occurred, i.e., it does not include a reaction that, had it occurred in a more severe form, might have caused death.

6.1.5 Unanticipated Problems

Definition:

- unexpected (in terms of nature, severity, or frequency) given (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and (b) the characteristics of the subject population being studied;
- related or possibly related to participation in the research ("possibly related" means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and
- suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

6.1.6 Noncompliance

Definition: failure to follow any applicable regulation or institutional policies that govern human subjects research or failure to follow the determinations of the

IRB. Noncompliance may occur due to lack of knowledge or due to deliberate choice to ignore regulations, institutional policies, or determinations of the IRB.

6.1.7 Serious Noncompliance

Definition: noncompliance that materially increases risks, that results in substantial harm to subjects or others, or that materially compromises the rights or welfare of participants.

6.1.8 Protocol Exceptions

Definition: A planned deviation from the approved protocol that are under the research team's control. Exceptions apply only to a single participant or a singular situation.

Local IRB pre-approval of all protocol exceptions must be obtained prior to the event. For secondary sites, the Washington University PI will issue approval of the exception, but it must also be submitted to the local IRB with documentation of approval forwarded to Washington University. Washington University IRB approval is not required for protocol exceptions occurring at secondary sites.

6.2 Reporting to the Human Research Protection Office (HRPO) at Washington University

The PI is required to promptly notify the IRB of the following events:

- Any unanticipated problems involving risks to participants or others which occur at WU, any BJH or SLCH institution, or that impacts participants or the conduct of the study.
- Noncompliance with federal regulations or the requirements or determinations of the IRB.
- Receipt of new information that may impact the willingness of participants to participate or continue participation in the research study.

These events must be reported to the IRB within **10 working days** of the occurrence of the event or notification to the PI of the event. The death of a research participant that qualifies as a reportable event should be reported within **1 working day** of the occurrence of the event or notification to the PI of the event.

6.3 Reporting to the Quality Assurance and Safety Monitoring Committee (QASMC) at Washington University

The PI is required to notify the QASMC of any unanticipated problem occurring at WU or any BJH or SLCH institution that has been reported to and acknowledged by HRPO as reportable. (Unanticipated problems reported to HRPO and withdrawn during the review process need not be reported to QASMC.)

QASMC must be notified within **10 days** of receipt of IRB acknowledgment via email to a QASMC auditor.

6.4 Reporting Requirements for Secondary Sites

The research team at each secondary site is required to promptly notify the Washington University PI and research coordinator of all reportable events (as described in Section 7.6)

within **1 working day** of the occurrence of the event or notification of the secondary site's PI of the event. This notification may take place via email if there is not yet enough information for a formal written report (using either an FDA MedWatch form if required or an institutional SAE reporting form if not). A formal written report must be sent to the Washington University PI and research coordinator within **10 working days** of the occurrence of the event or notification of the secondary site's PI of the event. The death of a research participant that qualifies as a reportable event should be reported within **1 working day** of the occurrence of the event or notification of the secondary site's PI of the event.

The research team at a secondary site is responsible for following its site's guidelines for reporting applicable events to its site's IRB according to its own institutional guidelines.

6.5 Reporting to Secondary Sites

The Washington University PI (or designee) will notify the research team at each secondary site of all reportable events that have occurred at other sites within **10 working days** of the occurrence of the event or notification of the PI of the event. This includes events that take place both at Washington University and at other secondary sites, if applicable.

6.6 Timeframe for Reporting Required Events

Adverse events will be tracked for 6 months following the last day of SBRT. Please note, only acute adverse events will be tracked. Adverse events will be followed for six months, and patients will be followed for up to eight months. For the purposes of this protocol, adverse events collected and documented on CRFs are non-hematologic acute grade 3 or higher toxicities that did not predate SBRT and are probably or definitely attributable to treatment. For patients receiving treatment to abdominal sites, such gastrointestinal toxicities of concern include (but are not limited to): severe pain, severe nausea or diarrhea, severe constipation, and/or gastrointestinal hemorrhage, stenosis, ulceration, fistula, perforation, etc. Patients undergoing treatment to non-liver abdominal lesions will also be assessed for hepatobiliary toxicity, such as biliary stenosis, gallbladder obstruction, radiation induced liver disease (RILD), etc. Regardless of treatment site, skin toxicity will be tabulated according to the CTCAE v4.0 criteria.

7.0 CORRELATIVE STUDIES

Quality of life (QOL) will be assessed using the EORTC QLQ-C30 questionnaire, which will be administered pre-treatment and at 4-8 weeks and 6-8 months post-completion of SBRT.

8.0 STUDY CALENDAR

Screening tests must occur no more than 8 weeks prior to registration.

	Screening	Baseline	D1	D2	D3	D4	D5	4-8 wks post- SBRT ²	3-5 mos post- SBRT	6-8 mos post- SBRT
Informed consent	X									
Medical history	X									
Volumetric imaging ¹	X							X	X	X
CBC	X									
CMP	X									
Pregnancy test ³	X									
EORTC QLQ-C30		X						X		X
Randomization		X								
SBRT ⁴			X	X	X	X	X			
AE assessment ⁵								X	X	X

1. CT, MRI, or PET are acceptable as per routine clinical evaluation at the discretion of the treating physician
2. Window is 5-10 weeks post-completion of SBRT
3. Women of childbearing potential only
4. SBRT will be given over five fractions delivered once daily or once every other day for a period of one to two weeks, for a total of five treatments
5. For the purposes of this protocol, acute adverse events collected and documented on CRFs are acute non-hematologic grade 3 or higher toxicities that did not predate SBRT and are probably or definitely attributable to treatment.

9.0 DATA SUBMISSION SCHEDULE

Case report forms with appropriate source documentation will be completed according to the schedule listed in this section.

Case Report Form	Submission Schedule
Original Consent Form	Prior to registration
On-Study Form	Prior to starting treatment
Toxicity Form	Continuous
Treatment Summary Form	Completion of treatment
Follow Up Form	6 weeks 4-8 weeks 3-5 months 6-8 months
Tumor Measurement Form	Baseline 6 weeks 3 months 6 months

EORTC-QLQ C30	Baseline
	6 weeks
	6 months

Any queries generated by Washington University must be responded to within 28 days of receipt by the participating site. The Washington University research team will conduct a regular review of data status at all secondary sites, with appropriate corrective action to be requested as needed.

10.0 MEASUREMENT OF EFFECT

10.1 Antitumor Effect – Solid Tumors

For the purposes of this study, patients should be re-evaluated for response at 4-8 weeks, 3-5 months, and 6-8 months post-completion of SBRT.

Response and progression will be evaluated in this study using the new international criteria proposed by the revised Response Evaluation Criteria in Solid Tumors (RECIST) guideline (version 1.1) [Eur J Ca 45:228-247, 2009]. Changes in the largest diameter (unidimensional measurement) of the tumor lesions and the shortest diameter in the case of malignant lymph nodes are used in the RECIST criteria.

10.2 Disease Parameters

Measurable disease: Measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded) as >20 mm by chest x-ray, as >10 mm with CT scan, or >10 mm with calipers by clinical exam. All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters).

Malignant lymph nodes: To be considered pathologically enlarged and measurable, a lymph node must be >15 mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and followed.

Non-measurable disease: All other lesions (or sites of disease), including small lesions (longest diameter <10 mm or pathological lymph nodes with ≥ 10 to <15 mm short axis), are considered non-measurable disease. Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonitis, inflammatory breast disease, and abdominal masses (not followed by CT or MRI), are considered as non-measurable.

Note: Cystic lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts.

‘Cystic lesions’ thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same patient, these are preferred for selection as target lesions.

Target lesions: All measurable lesions, up to a maximum size of a single abdominal site that can reasonably be encompassed in a single treatment field, should be identified as target lesions and recorded and measured at baseline. Target lesions should be selected on the basis of their size

(lesions with the longest diameter), be representative of all involved organs, but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion, which can be measured reproducibly should be selected. A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. If lymph nodes are to be included in the sum, then only the short axis is added into the sum. The baseline sum diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

Non-target lesions: All other lesions (or sites of disease) including any measurable lesions apart from the target lesion should be identified as non-target lesions and should also be recorded at baseline. Measurements of these lesions are not required, but the presence, absence, or in rare cases unequivocal progression of each should be noted throughout follow-up.

10.3 Methods for Evaluation of Measurable Disease

All measurements should be taken and recorded in metric notation using a ruler or calipers. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 4 weeks before the beginning of the treatment.

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging-based evaluation is preferred to evaluation by clinical examination unless the lesion(s) being followed cannot be imaged but are assessable by clinical exam.

Clinical lesions: Clinical lesions will only be considered measurable when they are superficial (e.g., skin nodules and palpable lymph nodes) and ≥ 10 mm diameter as assessed using calipers (e.g., skin nodules). In the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.

Conventional CT and MRI: This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm or less. If CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (e.g. for body scans).

Use of MRI remains a complex issue. MRI has excellent contrast, spatial, and temporal resolution; however, there are many image acquisition variables involved in MRI, which greatly impact image quality, lesion conspicuity, and measurement. Furthermore, the availability of MRI is variable globally. As with CT, if an MRI is performed, the technical specifications of the scanning sequences used should be optimized for the evaluation of the type and site of disease. Furthermore, as with CT, the modality used at follow-up should be the same as was used at baseline and the lesions should be measured/assessed on the same pulse sequence. It is beyond the scope of the RECIST guidelines to prescribe specific MRI pulse sequence parameters for all scanners, body parts, and diseases. Ideally, the same type of scanner should be used and the image acquisition protocol should be followed as closely as possible to prior scans. Body scans should be performed with breath-hold scanning techniques, if possible.

PET-CT: At present, the low dose or attenuation correction CT portion of a combined PET-CT is not always of optimal diagnostic CT quality for use with RECIST measurements. However, if the site can document that the CT performed as part of a PET-CT is of identical diagnostic quality

to a diagnostic CT (with IV and oral contrast), then the CT portion of the PET-CT can be used for RECIST measurements and can be used interchangeably with conventional CT in accurately measuring cancer lesions over time. Note, however, that the PET portion of the CT introduces additional data which may bias an investigator if it is not routinely or serially performed.

Ultrasound: Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement. Ultrasound examinations cannot be reproduced in their entirety for independent review at a later date and, because they are operator dependent, it cannot be guaranteed that the same technique and measurements will be taken from one assessment to the next. If new lesions are identified by ultrasound in the course of the study, confirmation by CT or MRI is advised. If there is concern about radiation exposure at CT, MRI may be used instead of CT in selected instances.

Endoscopy, Laparoscopy: The utilization of these techniques for objective tumor evaluation is not advised. However, such techniques may be useful to confirm complete pathological response when biopsies are obtained or to determine relapse in trials where recurrence following complete response (CR) or surgical resection is an endpoint.

Tumor markers: Tumor markers alone cannot be used to assess response. If markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response. Specific guidelines for both CA-125 response (in recurrent ovarian cancer) and PSA response (in recurrent prostate cancer) have been published [JNCI 96:487-488, 2004; J Clin Oncol 17, 3461-3467, 1999; J Clin Oncol 26:1148-1159, 2008]. In addition, the Gynecologic Cancer Intergroup has developed CA-125 progression criteria which are to be integrated with objective tumor assessment for use in first-line trials in ovarian cancer [JNCI 92:1534-1535, 2000].

Cytology, Histology: These techniques can be used to differentiate between partial responses (PR) and complete responses (CR) in rare cases (e.g., residual lesions in tumor types, such as germ cell tumors, where known residual benign tumors can remain).

The cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment when the measurable tumor has met criteria for response or stable disease is mandatory to differentiate between response or stable disease (an effusion may be a side effect of the treatment) and progressive disease.

FDG-PET: While FDG-PET response assessments need additional study, it is sometimes reasonable to incorporate the use of FDG-PET scanning to complement CT scanning in assessment of progression (particularly possible 'new' disease). New lesions on the basis of FDG-PET imaging can be identified according to the following algorithm:

- Negative FDG-PET at baseline, with a positive FDG-PET at follow-up is a sign of PD based on a new lesion.
- No FDG-PET at baseline and a positive FDG-PET at follow-up: If the positive FDG-PET at follow-up corresponds to a new site of disease confirmed by CT, this is PD. If the positive FDG-PET at follow-up is not confirmed as a new site of disease on CT, additional follow-up CT scans are needed to determine if there is truly progression occurring at that site (if so, the date of PD will be the date of the initial abnormal FDG-PET scan). If the positive FDG-PET at follow-up corresponds to a pre-existing site of disease on CT that is not progressing on the basis of the anatomic images, this is not PD.

- FDG-PET may be used to upgrade a response to a CR in a manner similar to a biopsy in cases where a residual radiographic abnormality is thought to represent fibrosis or scarring. The use of FDG-PET in this circumstance should be prospectively described in the protocol and supported by disease-specific medical literature for the indication. However, it must be acknowledged that both approaches may lead to false positive CR due to limitations of FDG-PET and biopsy resolution/sensitivity.

Note: A 'positive' FDG-PET scan lesion means one which is FDG avid with an uptake greater than twice that of the surrounding tissue on the attenuation corrected image.

10.4 Response Criteria

10.4.1 Evaluation of Target Lesions

As that this is a local therapy protocol, non-target changes in disease will not be scored.

Complete Response (CR): Disappearance of the target lesion. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm.

Partial Response (PR): At least a 30% decrease in the (sum of the) diameter of the target lesion(s), taking as reference the baseline sum diameters.

Progressive Disease (PD): At least a 20% increase in the sum of the diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm.

Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.

10.4.2 Evaluation of Best Overall Response

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for progressive disease the smallest measurements recorded since the treatment started). The patient's best response assignment will depend on the achievement of both measurement and confirmation criteria.

For Patients with Measurable Disease (i.e., Target Disease)

Target Lesions	Non-Target Lesions	New Lesions	Overall Response	Best Overall Response when Confirmation is Required*
CR	CR	No	CR	>4 wks. Confirmation**
CR	Non-CR/Non-PD	No	PR	>4 wks. Confirmation**
CR	Not evaluated	No	PR	
PR	Non-CR/Non-PD/not evaluated	No	PR	
SD	Non-CR/Non-PD/not evaluated	No	SD	Documented at least once >4 wks. from baseline**
PD	Any	Yes or No	PD	no prior SD, PR or CR
Any	PD***	Yes or No	PD	
Any	Any	Yes	PD	
<p>* See RECIST 1.1 manuscript for further details on what is evidence of a new lesion.</p> <p>** Only for non-randomized trials with response as primary endpoint.</p> <p>*** In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as disease progression.</p> <p>Note: Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as “symptomatic deterioration.” Every effort should be made to document the objective progression even after discontinuation of treatment.</p>				

10.4.3 Duration of Response

Duration of overall response: The duration of overall response is measured from the time measurement criteria are met for CR or PR (whichever is first recorded) until the first date that recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded since the treatment started).

The duration of overall CR is measured from the time measurement criteria are first met for CR until the first date that progressive disease is objectively documented.

Duration of stable disease: Stable disease is measured from the start of the treatment until the criteria for progression are met, taking as reference the smallest measurements recorded since the treatment started, including the baseline measurements.

10.4.4 Progression-Free Survival

PFS is defined as the duration of time from start of treatment to time of progression or death, whichever occurs first.

11.0 DATA AND SAFETY MONITORING

In compliance with the Washington University Institutional Data and Safety Monitoring Plan, an

independent Data and Safety Monitoring Committee (DSMC) will be specifically convened for this trial to review toxicity data at least every 6 months following the activation of the first secondary site. A DSMC will consist of no fewer than 3 members including 2 clinical investigators and a biostatistician. Like investigators, DSMC members are subject to the Washington University School of Medicine policies regarding standards of conduct. Individuals invited to serve on the DSMC will disclose any potential conflicts of interest to the trial principal investigator and/or appropriate university officials, in accordance with institution policies. Potential conflicts that develop during a trial or a member's tenure on a DSMC must also be disclosed.

The DSM report will be prepared by the study statistician with assistance from the study team, will be reviewed by the DSMC, and will be submitted to the Washington University Quality Assurance and Safety Monitoring Committee (QASMC). This report will include:

- HRPO protocol number, protocol title, Principal Investigator name, data coordinator name, regulatory coordinator name, and statistician
- Date of initial HRPO approval, date of most recent consent HRPO approval/revision, date of HRPO expiration, date of most recent QA audit, study status, and phase of study
- History of study including summary of substantive amendments; summary of accrual suspensions including start/stop dates and reason; and summary of protocol exceptions, error, or breach of confidentiality including start/stop dates and reason
- Study-wide target accrual and study-wide actual accrual including numbers from participating sites
- Protocol activation date at each participating site
- Average rate of accrual observed in year 1, year 2, and subsequent years at each participating site
- Expected accrual end date, accrual by site, and accrual by cohort
- Objectives of protocol with supporting data and list the number of participants who have met each objective
- Measures of efficacy
- Early stopping rules with supporting data and list the number of participants who have met the early stopping rules
- Summary of toxicities at all participating sites separated by cohort
- Abstract submissions/publications
- Summary of any recent literature that may affect the safety or ethics of the study

Further DSMC responsibilities are described in the DSMC charter.

Until such a time as the first secondary site activates this protocol, a semi-annual DSM report to be prepared by the study team will be submitted to the QASM Committee beginning 6 months after study activation at Washington University.

The study principal investigator and coordinator will monitor for serious toxicities on an ongoing basis. Once the principal investigator or coordinator becomes aware of an adverse event, the AE will be reported to the HRPO and QASMC according to institutional guidelines (please refer to Section 6.0).

Refer to the Washington University Quality Assurance and Data Safety Monitoring Committee Policies and Procedures for full details on the responsibilities of the DSMC at <https://siteman.wustl.edu/wp-content/uploads/2015/10/QASMC-Policies-and-Procedures-03.31.2015.pdf>

12.0 AUDITING

As coordinating center of this trial, Washington University, via the Quality Assurance and Safety Monitoring Committee (QASMC) will monitor each participating site to ensure that all protocol requirements are being met; that applicable federal regulations are being followed; and that best practices for patient safety and data collection are being followed per protocol. Participating sites will be asked to send copies of all audit materials, including source documentation. The audit notification will be sent to the Washington University Research Patient Coordinator, who will obtain the audit materials from the participating institution.

Notification of an upcoming audit will be sent to the research team one month ahead of the audit. Once accrual numbers are confirmed, and approximately 30 days prior to the audit, a list of the cases selected for review (up to 10 for each site) will be sent to the research team. However, if during the audit the need arises to review cases not initially selected, the research team will be asked to provide the additional charts within two working days.

Items to be evaluated include:

- Subject screening and enrollment
- Reporting of adverse events
- Maintenance of HIPAA compliance
- Completeness of regulatory documentation
- Completeness of participant documentation
- Acquisition of informed consent
- IRB documentation
- Issues of protocol adherence

Additional details regarding the auditing policies and procedures can be found at <https://siteman.wustl.edu/wp-content/uploads/2015/10/QASMC-Policies-and-Procedures-03.31.2015.pdf>

13.0 STATISTICAL CONSIDERATIONS

13.1 Stopping Criteria

Stopping criteria will be defined as follows. If at any point in trial enrollment, >10 out of the first 30 patients, or >20 out of the first 60 patients experience symptoms of G3 or greater toxicity that is probably or definitely attributable to and did not pre-date SBRT, the trial will be suspended. Study accrual will not be stopped early for futility. Symptoms that pre-dated SBRT will not be count towards stopping criteria (example: a patient with daily, activity-limiting gastrointestinal pain prior to and after SBRT will not be scored as G3 toxicity, however new, severe pain within the treatment field, limiting self care would count towards stopping criteria). If at any time a grade 5 toxicity (death) is observed that is probably or definitely attributable to treatment, accrual will be suspended and the event will be reviewed by the principal investigator. Since patients accruing to the trial have metastatic disease, it is anticipated that deaths unrelated to the trial may be observed. Death that is felt either due to disease progression or patient comorbidity will not be scored as grade 5 toxicity and will not result in trial suspension.

13.2 Sample Size

Our primary objective will be to demonstrate that online-adaptive MRI-guided SBRT reduces

acute non-hematologic Grade 3 or higher acute treatment-related toxicity from historical rates of 25-35% to <10% acute non-hematologic Grade 3 or higher toxicity. As a phase II study, the sample size is determined based on statistical power calculations. We utilize a one-sided test for independent proportions based on the historical estimate of 30% toxicity versus our estimated 10% toxicity. We will also conduct an interim analysis at 50 patients. Utilizing O'Brien Fleming calculations for interim analysis we would need a total of 100 patients will be enrolled to the study, with randomization to two treatment arms. This will achieve approximately 73% power (with $\alpha = 0.05$) to detect a significant decrease in G3 toxicity. If we obtain significant results with the first 50 patients we will stop the trial and conclude that the online adaptive arm significantly reduces toxicity over the conventional arm. In arm A, patients will be treated using online-adaptive MRI-guided SBRT, versus arm B, where abdominal SBRT with non-adaptive, daily image-guided localization will be utilized. All patients will be treated at a single abdominal site that can reasonably be encompassed in a single treatment field. Radiation therapy treatment of sites outside of the abdomen while the patient is on-trial is acceptable. However, included patients will have three or fewer sites of progressing disease.

For our secondary objectives, our goal will be to report the description of treatment adaptation and quality of life associated with online adaptive MRI guided SBRT. Given that no prior data exists for online, MRI-guided SBRT, we will report descriptive statistics for treatment adaptation, tumor response rate, in-field control rate, progression free survival, disease free survival, overall survival, time for delivery of therapy, and quality of life metrics.

13.3 Primary Objective

Demonstrate that online, adaptive, MRI-guided SBRT to the non-liver abdomen reduces toxicity by confirming that adaptive treatment reduces acute non-hematologic Grade 3 or greater toxicity from 30% to <10% when compared to non-adaptive SBRT.

13.4 Secondary Objectives

- Determine the tumor response rate at three months utilizing tests for proportion.
- Determine the progression free survival rates and disease-free survival rate utilizing Kaplan-Meier methodology.
- Determine the rate of overall survival utilizing Kaplan-Meier methodology.
- Determine the patient-reported quality of life pre-treatment, at six weeks post-treatment, and at six months post-treatment, using EORTC-30 criteria. We will utilize both paired t-tests and repeated measures ANOVA to analyze QOL data.

13.5 Statistical Analysis Plan

Our principal objective in this trial will be to determine the rate of treatment-induced, acute toxicity of online, adaptive MRI-guided SBRT with MRI simulation and MRI gating for treatment of oligometastatic disease of the non-liver abdomen when compared to SBRT with daily image-guided localization. Statistical analysis will be powered to detect a reduction of toxicity from 35% acute non-hematologic Grade 3 or greater toxicity to 10% acute non-hematologic Grade 3 or greater toxicity using online-adaptive therapy. Statistical analysis will be one-sided test for independent proportions.

Given that limited prior data exists for online adaptive, MRI-guided SBRT, we will also report descriptive statistics for treatment adaptation, tumor response rate, in-field control rate,

progression free survival, disease free survival, overall survival, time for delivery of therapy, and quality of life metrics.

14.0 MULTICENTER REGULATORY REQUIREMENTS

Washington University requires that each participating site sends its informed consent document to be reviewed and approved by the Washington University Regulatory Coordinator (or designee) prior to IRB/IEC submission.

Site activation is defined as when the secondary site has received official written documentation from the coordinating center that the site has been approved to begin enrollment. At a minimum, each participating institution must have the following documents on file at Washington University prior to study activation:

- Documentation of IRB approval of the study in the form of a letter or other official document from the participating institution's IRB. This documentation must show which version of the protocol was approved by the IRB.
- Documentation of IRB approval of an informed consent form. The consent must include a statement that data will be shared with Washington University, including the Quality Assurance and Safety Monitoring Committee (QASMC), the DSMC (if applicable), and the Washington University study team.
- Documentation of FWA, signed FDA Form 1572 (if applicable), and the CVs of all participating investigators.
- Protocol signature page signed and dated by the investigator at each participating site.

The coordinating center Principal Investigator (or designee) is responsible for disseminating to the participating sites all study updates, amendments, reportable adverse events, etc. Protocol/consent modifications and IB updates will be forwarded electronically to the secondary sites within 4 weeks of obtaining Washington University IRB approval. Activated secondary sites are expected to submit protocol/consent/IB modifications to their local IRBs within 4 weeks of receipt unless otherwise noted. Upon the secondary sites obtaining local IRB approval, documentation of such shall be sent to the Washington University study team within 2 weeks of receipt of approval.

Documentation of participating sites' IRB approval of annual continuing reviews, protocol amendments or revisions, all SAE reports, and all protocol violations/deviations/exceptions must be kept on file at Washington University.

The investigator or a designee from each institution must participate in a regular conference call to update and inform regarding the progress of the trial.

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APPENDIX A: ECOG Performance Status Scale

Grade	Description
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (e.g., light housework, office work).
2	In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead.